

4-Acetamido-3,3,5,5-[²H₄]-2,2,6,6-tetra([²H₃]methyl)piperidin-1-yloxyl 0.33-hydrate

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Received 15 June 2006

Accepted 27 June 2006

Online 11 August 2006

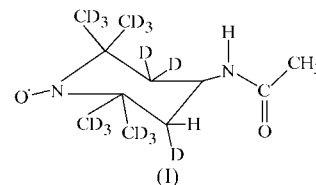
The asymmetric unit of the title compound, C₁₁H₅-D₁₆N₂O₂·0.33H₂O, is formed by three crystallographically independent piperidin-1-yloxyl molecules and a molecule of water. The molecules are crosslinked by nine hydrogen bonds into layers parallel with the *ac* plane. The water molecule contributes to the stability of the low-symmetry arrangement by four hydrogen bonds.

Comment

Recent advances in electron spin resonance (ESR) technology [*i.e.* extension of ESR to high fields and very high frequencies (HF-ESR), and the development of two-dimensional Fourier transform ESR imaging with very short pulsed field gradients] bring very powerful experimental techniques to bear for the desired analysis of the nanosecond-scale dynamics of macromolecular systems (LaConte *et al.*, 2002). The nitroxide radical 2,2,6,6-tetramethylpiperidin-1-yloxyl is a favourite spin label for site-directed mutagenesis of proteins, with the aim of following local motion in macromolecules. Intact interaction of the magnetic moment of an unpaired electron with the nuclear magnetic moment of nitrogen alone gives, in principle, a simple and sharp ESR spectrum. However, magnetic moments of hydrogen nuclei of methyl groups closely surrounding the nitroso group invoke undesired hyperfine interactions. This effect can be suppressed by deuteration of the piperidine ring, because of the smaller magnetic moment of the deuterium nucleus in comparison with a proton. It significantly simplifies the analysis of both fast- and slow-motion spectra. The method has broad utilization in biological (Bennati & Prisner, 2005), physicochemical (Mizuochi *et al.*, 1997) or synthetic (Bossmann *et al.*, 1996) studies.

The title compound, (I), belongs to this group of stable radicals and has been used in our institute as a paramagnetic tracer for electron spin resonance imaging (ESRI) for moni-

toring diffusion processes, with numerous practical applications, such as drug delivery systems and transport across membranes. It has also contributed significantly to understanding polymer dynamics (Pilař *et al.*, 1999).



The compound crystallizes in the centrosymmetric space group $P\bar{1}$. Three independent molecules, *A*, *B* and *C* (the letters are appended to the atom labels), and one molecule of water were refined in the asymmetric unit. An overall view of the first molecule, with displacement ellipsoids and labelling scheme, is shown in Fig. 1. The main geometric features of all molecules are given in Tables 2 and 3.

The main part of the compound, the piperidine ring, adopts a chair conformation, with angles between the planes C2/C3/C5/C6 and C2/N1/C6 of 31.7 (1), 30.6 (1) and 33.4 (1)° for molecules *A*, *B* and *C*, respectively, and between the planes C2/C3/C5/C6 and C3/C4/C5 of 52.2 (1), 53.9 (1) and 52.5 (1)°, respectively. This is in agreement with piperidine ring puckering observed in another structure with a methacrylamide substituent (Duskova *et al.*, 2006) and fits well with the average geometry of piperidine rings resulting from 114 hits found in the Cambridge Structural Database (Version 5.26; Allen, 2002). The linked acetamine chain (CH₃CONH-) occupies an equatorial position with respect to the ring and is almost ideally planar in all three molecules.

In order to elucidate the influence of crystal packing on molecular conformation, the symmetrically independent molecules *A*, *B* and *C* were superimposed on all the non-H atoms using the program package *CCP4* (Collaborative Computational Project, Number 4, 1994). The resulting r.m.s.

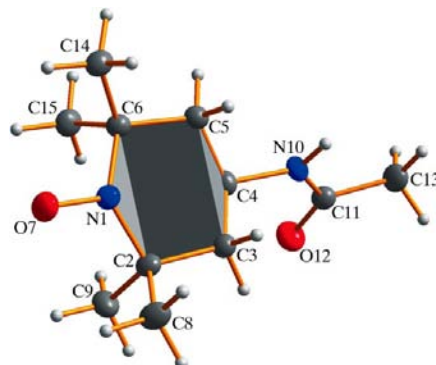


Figure 1

The atom-numbering scheme for molecule *A*. The interplanar angles characterizing the chair conformation of the piperidine ring are highlighted. Displacement ellipsoids are drawn at the 50% probability level. An identical numbering scheme applies to molecules *B* and *C*. For the purpose of this figure, the suffixes of the atom names identifying individual molecules have been omitted.

deviations were 0.055, 0.073 and 0.071 Å for *A*–*B*, *A*–*C* and *B*–*C* alignments of all non-H atoms, respectively. The largest deviation, the O12A··O12C distance of 0.264 Å, corresponding to about a 9° deviation in the C=O bond direction, is caused by different directions of hydrogen bonds formed by carbonyl atom O12 (Fig. 2). This is in accord with different values of the C3–C4–N10–C11 torsion angle of –91.0 (2), 94.4 (2) and 99.8 (2)° for molecules *A*, *B* and *C*, respectively. Other differences are observed in the conformations of the methyl groups of C8, C9 and C13. The angular differences between the extreme cases of orientations of the methyl groups (Fig. 2) are *ca* 24.1, 9.7 and 7.7° for the C13, C9 and C8 methyl groups, respectively. This is probably caused by stress induced by the hydrogen bonds. Atoms O12 and N10 of molecules *A*, *B* and *C* are involved in strong hydrogen bonding and the H atoms on atoms C13 and C9 of molecule *C* and on C8 of molecule *A* participate in weak intermolecular interactions. Surprisingly, only the single oxygen radical of molecule *C* is involved in intermolecular interactions defining the arrangement of the molecules in the crystal structure. It forms a strong hydrogen contact to a water molecule and a weak one to methyl atom C13 of molecule *C*. The oxygen radicals O7 of the other two molecules (*A* and *B*) do not form any hydrogen bonds in the crystal structure. This behaviour is different from that of an analogous compound, 3,3,5,5-tetra([²H₄]-4-methacrylamido-2,2,6,6-tetra([²H₃]methyl)piperidin-1-yloxy) (Duskova *et al.*, 2006), where the oxygen radical plays an essential role in the formation of a chain of molecules.

The mobilities of D atoms surrounding the nitroxyl group are significantly restricted, so that one C–D bond of each deuterated methyl group tends to orient parallel to the N–O bond (antiparallel dipoles). However, this cannot be fully satisfied, due to the puckering of the piperidine ring. Considering molecule *A*, the nitroso groups is directed between two methyl groups, resulting in a C8··C14 distance

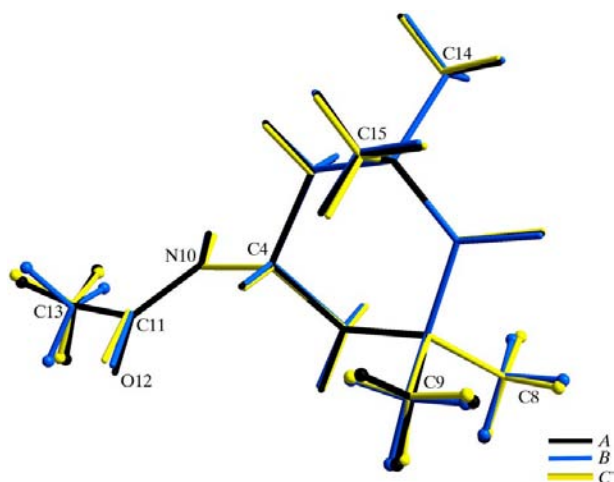


Figure 2

The overlap of molecules *A*, *B* and *C*. Significant differences in the conformations of the methyl groups are correlated with rotation of the carbonyl C11=O12 group. H and D atoms of the most flexible methyl groups are drawn as spheres.

of 4.679 (2) Å, compared with a distance of 3.517 (2) Å for the opposite pair of atoms, C9 and C15. Viewed in the direction of the nitroxide bond, the methyl groups form a trapezoid with an approximate mirror symmetry. In spite of this, the deuterated methyl groups are rotated so that the D atoms are divided into three groups with almost identical distances to the oxygen radical. The closest four D atoms in all three molecules have distances to nitroso atom O7 in the range 2.48–2.71 Å, the next four in the range 2.95–3.44 Å, and the last four methyl D atoms are at distances in the range 3.67–3.82 Å. The axial D atoms on C3 and C5 have identical distances of 3.90–3.93 Å. Irrespective of the steric hindrances imposed by the 2,2,6,6 methyl groups, the nitroxide radical forms two hydrogen bonds, *viz.* to a solvent water molecule and to a methyl group of the neighboring antiparallel-oriented molecule.

Molecules *A*, *B* and *C* are joined *via* one weak and four strong hydrogen bonds, with hydrogen–acceptor distances (Å) N10A–H··O12B = 2.01 (2), N10C–H··O12A = 1.97 (2), N10B–H··O1(water) = 2.06 (2), O12C··H–O1(water) = 1.94 (3) and C13C–H··O12A = 2.65. In this way, chains of molecules ···B···A···C···O···B··· are generated parallel to the *c* direction (Fig. 3). Another set of three hydrogen bonds connects these chains into layers parallel with *ab*. These involve hydrogen bonds C13C–H··O7C = 2.65 Å, O1(water)–H··O7C = 2.00 (3) Å and C9C–H··O1(water) = 2.61 (2) Å (Fig. 3).

A very weak C–H··O contact of 2.57 (2) Å between molecules *A* and *B* connects two neighbouring layers, forming bilayers in the *b* direction. Neighbouring bilayers related by a centre of symmetry interact only *via* van der Waals contacts between pairs of molecules *A*–*B* and *B*–*A*, *i.e.* by weak polar interactions of atom C5B and methyl groups C14B and C15B with atom O7A, and also of methyl groups C14A and C15A with amino group N10B.

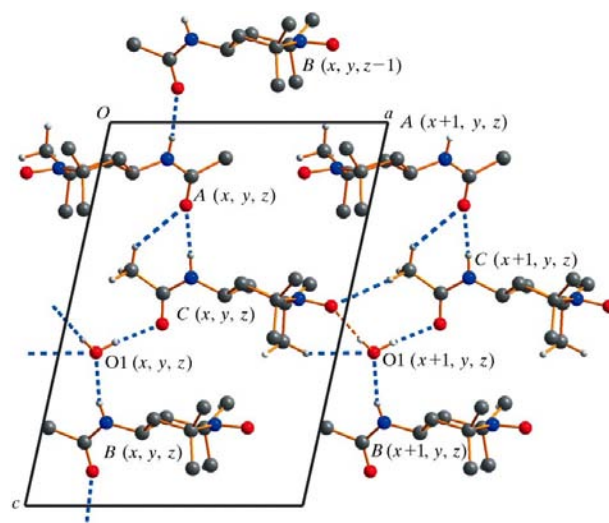


Figure 3

Part of the crystal structure of (I), showing the molecular packing. Symmetrically independent molecules are marked by capital letters and by their respective symmetry operators. Dashed lines indicate hydrogen bonds which are responsible for formation of the layer parallel to *ac*.

Experimental

4-Acetamido-3,3,5,5-[²H₄]-2,2,6,6-tetra([²H₃]methyl)piperidine (1 g), sodium ethylenediaminetetraacetate (0.1 g) and sodium tungstate dihydrate (0.1 g) were dissolved in methanol (5 ml) and water (3 ml) with 30% hydrogen peroxide (1.7 ml). The mixture was kept at laboratory temperature for 4 d. After the methanol had evaporated, the product was recrystallized from a dichloromethane–hexane mixture (1:1).

Crystal data

C ₁₁ H ₅ D ₁₆ N ₂ O ₂ ·0.33H ₂ O	$V = 1851.41 (9) \text{ \AA}^3$
$M_r = 235.34$	$Z = 6$
Triclinic, $P\bar{1}$	$D_x = 1.266 \text{ Mg m}^{-3}$
$a = 10.6940 (3) \text{ \AA}$	Mo $K\alpha$ radiation
$b = 11.7120 (3) \text{ \AA}$	$\mu = 0.08 \text{ mm}^{-1}$
$c = 16.0480 (5) \text{ \AA}$	$T = 150 \text{ K}$
$\alpha = 109.351 (1)^\circ$	Irregular, red
$\beta = 101.678 (1)^\circ$	$0.2 \times 0.1 \times 0.1 \text{ mm}$
$\gamma = 90.325 (1)^\circ$	

Data collection

Nonius KappaCCD area-detector diffractometer	8420 independent reflections
φ and ω scans	6918 reflections with $I > 2\sigma(I)$
35956 measured reflections	$R_{\text{int}} = 0.055$
	$\theta_{\text{max}} = 27.5^\circ$

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.1025P)^2 + 1.9749P]$
$R[F^2 > 2\sigma(F^2)] = 0.048$	where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2) = 0.140$	$(\Delta/\sigma)_{\text{max}} = 0.001$
$S = 1.05$	$\Delta\rho_{\text{max}} = 0.29 \text{ e \AA}^{-3}$
8420 reflections	$\Delta\rho_{\text{min}} = -0.28 \text{ e \AA}^{-3}$
663 parameters	
H atoms treated by a mixture of independent and constrained refinement	

Table 1

Hydrogen-bond geometry (\AA , $^\circ$).

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
N10A–H18A \cdots O12B ⁱ	0.86 (2)	2.01 (2)	2.865 (2)	173.3 (9)
N10B–H18B \cdots O1	0.83 (2)	2.06 (2)	2.862 (2)	165 (1)
N10C–H18C \cdots O12A	0.89 (2)	1.97 (2)	2.859 (2)	173.3 (9)
O1–H1 \cdots O12C	0.84 (3)	1.94 (3)	2.778 (2)	174 (2)
O1–H2 \cdots O7C ⁱⁱ	0.89 (3)	2.00 (3)	2.890 (2)	174 (2)
C13C–H19C \cdots O7C ⁱⁱ	0.96	2.65	3.562 (2)	158
C13C–H21C \cdots O12A	0.96	2.64	3.474 (2)	146
C8A–H6A \cdots O12B ⁱⁱⁱ	1.01 (2)	2.57 (2)	3.516 (2)	156 (1)
C9C–H10C \cdots O1 ^{iv}	1.02 (2)	2.61 (2)	3.540 (2)	151 (2)

Symmetry codes: (i) $x, y, z - 1$; (ii) $x - 1, y, z$; (iii) $-x, -y - 1, -z + 1$; (iv) $x + 1, y, z$.

Two strong reflections, 001 and 010, were omitted from the refinement because the beam stop influenced the accuracy of their measurement. The D atoms of the piperidine ring were refined as H atoms. First, all H atoms were added in their ideal geometric positions, as implemented in *SHELXL97* (Sheldrick, 1997). In subsequent steps, all constraints for D atoms were released for free refinement, including their isotropic displacement parameters. The H atoms on atom C13 in all three molecules were refined as a rigid group, with $U_{\text{iso}}(\text{H}) = 1.5U_{\text{eq}}(\text{C})$. The positions of the H atoms of a single water molecule were clearly identified in the electron-density map and were refined freely with isotropic displacement parameters.

Data collection: *COLLECT* (Nonius, 1998) and *DENZO* (Otwinowski & Minor, 1997); cell refinement: *COLLECT* and *DENZO*; data reduction: *COLLECT* and *DENZO*; program(s) used

Table 2

Comparison of bond lengths (\AA) in the three molecules of (I).

	A	B	C
N1–O7	1.287 (2)	1.290 (2)	1.290 (2)
N1–C6	1.500 (2)	1.498 (2)	1.498 (2)
N1–C2	1.497 (2)	1.494 (2)	1.497 (2)
C2–C9	1.532 (2)	1.525 (2)	1.532 (2)
C2–C3	1.531 (2)	1.533 (2)	1.533 (2)
C2–C8	1.528 (2)	1.527 (2)	1.527 (2)
C3–C4	1.525 (2)	1.524 (2)	1.525 (2)
C4–N10	1.461 (2)	1.460 (2)	1.462 (2)
C4–C5	1.520 (2)	1.523 (2)	1.517 (2)
C5–C6	1.530 (2)	1.531 (2)	1.531 (2)
C6–C15	1.534 (2)	1.532 (2)	1.534 (2)
C6–C14	1.529 (2)	1.524 (2)	1.526 (2)
N10–C11	1.339 (2)	1.331 (2)	1.333 (2)
C11–O12	1.235 (2)	1.238 (2)	1.239 (2)
C11–C13	1.504 (2)	1.507 (2)	1.510 (2)

Table 3

Comparison of bond angles ($^\circ$) in the three molecules of (I).

	A	B	C
O7–N1–C6	115.9 (1)	115.7 (1)	115.5 (1)
O7–N1–C2	115.8 (1)	115.8 (1)	116.1 (1)
C6–N1–C2	124.2 (1)	124.6 (1)	124.4 (1)
N1–C2–C9	109.1 (1)	109.5 (1)	109.5 (1)
N1–C2–C3	110.2 (1)	110.1 (1)	109.5 (1)
C9–C2–C3	111.8 (1)	111.1 (1)	111.2 (1)
N1–C2–C8	107.8 (1)	107.6 (1)	107.7 (1)
C9–C2–C8	109.2 (1)	109.5 (1)	110.0 (1)
C3–C2–C8	108.6 (1)	109.0 (1)	108.8 (1)
C4–C3–C2	114.4 (1)	113.7 (1)	113.5 (1)
N10–C4–C3	110.4 (1)	110.3 (1)	110.2 (1)
N10–C4–C5	109.2 (1)	110.3 (1)	109.3 (1)
C3–C4–C5	108.2 (1)	107.8 (1)	108.2 (1)
N1–C6–C15	109.4 (1)	109.1 (1)	108.5 (1)
N1–C6–C14	107.7 (1)	107.5 (1)	108.3 (1)
C15–C6–C14	109.6 (1)	109.8 (1)	109.1 (1)
N1–C6–C5	110.1 (1)	110.3 (1)	109.7 (1)
C15–C6–C5	111.1 (1)	111.6 (1)	112.1 (1)
C14–C6–C5	108.8 (1)	108.5 (1)	109.1 (1)
C11–N10–C4	123.2 (1)	122.5 (1)	123.8 (1)
O12–C11–N10	122.4 (1)	122.7 (1)	123.0 (1)
O12–C11–C13	121.9 (1)	121.2 (1)	121.3 (1)
N10–C11–C13	115.7 (1)	116.1 (1)	115.6 (1)

to solve structure: *SHELXS97* (Sheldrick, 1990); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *DIAMOND* (Brandenburg & Putz, 2005); software used to prepare material for publication: *SHELXL97* and *DIAMOND*.

This research was supported by the Grant Agency of the Czech Republic, project No. T400500402.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK3034). Services for accessing these data are described at the back of the journal.

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